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# Screening for Colorectal Cancer Using a Multitarget Stool DNA Test: Modeling the Effect of the Intertest Interval on Clinical Effectiveness

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## Abstract

**Colorectal cancer (CRC) screening with a multitarget stool DNA test was recently approved by the Food and Drug Administration. We used clinical effectiveness modeling to compare test intervals of 1, 3, or 5 years on CRC incidence and related mortality to help inform screening guidelines. Our results showed that screening every 3 years provides reasonable performance at acceptable cost.**

**Background:** A multitarget stool DNA (mt-sDNA) test was recently approved for colorectal cancer (CRC) screening for men and women, aged  $\geq 50$  years, at average risk of CRC. The guidelines currently recommend a 3-year interval for mt-sDNA testing in the absence of empirical data. We used clinical effectiveness modeling to project decreases in CRC incidence and related mortality associated with mt-sDNA screening to help inform interval setting. **Materials and Methods:** The Archimedes model (Archimedes Inc., San Francisco, CA) was used to conduct a 5-arm, virtual, clinical screening study of a population of 200,000 virtual individuals to compare the clinical effectiveness of mt-sDNA screening at 1-, 3-, and 5-year intervals compared with colonoscopy at 10-year intervals and no screening for a 30-year period. The study endpoints were the decrease in CRC incidence and related mortality of each strategy versus no screening. Cost-effectiveness ratios (US dollars per quality-adjusted life year [QALY]) of mt-sDNA intervals were calculated versus no screening. **Results:** Compared with 10-year colonoscopy, annual mt-sDNA testing produced similar reductions in CRC incidence (65% vs. 63%) and related mortality (73% vs. 72%). mt-sDNA testing at 3-year intervals reduced the CRC incidence by 57% and CRC mortality by 67%, and mt-sDNA testing at 5-year intervals reduced the CRC incidence by 52% and CRC mortality by 62%. At an average price of \$600 per test, the annual, 3-year, and 5-year mt-sDNA screening costs would be \$20,178, \$11,313, and \$7388 per QALY, respectively, compared with no screening. **Conclusion:** These data suggest that screening every 3 years using a multitarget mt-sDNA test provides reasonable performance at acceptable cost.

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**Keywords:** Archimedes, Colonoscopy, Guidelines, Model, Utility

## Introduction

The current guideline from the US Preventive Services Task Force recommends routine colorectal cancer (CRC) screening in individuals with average risk beginning at age 50 years and continuing until age 75.<sup>1</sup> Screening should then be individualized thereafter until age 85,

depending on the individual's overall health.<sup>1</sup> Despite the universal appreciation of the value of CRC screening and the availability of multiple screening options, CRC screening rates have remained suboptimal.<sup>2</sup> Optical colonoscopy, the reference method for all other screening strategies, provides a direct pancolonoscopic structural examination. Despite the effectiveness of colonoscopy, its usage in daily practice remains limited. Some patients might not have access to it, and others are reluctant or refuse the procedure; thus, compliance with colonoscopy remains low.<sup>2,3</sup> The colonoscopy results can also be affected by the quality of the bowel preparatory process, colorectal anatomy, and operator skill.<sup>4,5</sup> Furthermore, previously available noninvasive tests only assessed lesional bleeding, which, if present, can be erratic.

A simple, noninvasive, multitarget stool DNA (mt-sDNA)-based screening test (Cologuard; Exact Sciences, Madison, WI) with much

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greater sensitivity for the detection of both CRC and advanced precancerous lesions was thus developed to improve both noninvasive screening performance and screening compliance.<sup>6-8</sup> Cologuard consists of quantitative molecular assays to detect aberrantly methylated DNA (*NDRG4* and *BMP3*) and DNA mutations (*KRAS*) in stool plus a fecal hemoglobin immunoassay. It was approved by the US Food and Drug Administration in August 2014 for screening men and women aged  $\geq 50$  years with an average risk of CRC. The test results are analyzed using a logistic regression algorithm with a predefined cutoff value to provide a single dichotomous “positive” or “negative” test result.<sup>7,8</sup> Patients with “positive” results are referred for diagnostic colonoscopy and patients with “negative” findings continue with the average-risk CRC screening program and undergo screening again in the future.

The current guidelines recommend a 3-year interval for mt-sDNA-based testing<sup>9,10</sup>; however, the optimal testing interval for Cologuard is in development. In the absence of longitudinal data, the Agency for Healthcare Research and Quality has recommended modeling as the preferred method for setting initial test intervals, given the length, size, and complexity of the prospective studies that would be needed to address this question.<sup>11</sup> Comprehensive CRC disease state models mimic the known biology of CRC development in relation to patient factors, screening, and treatment strategies and can estimate clinical effectiveness by calculating the theoretical reductions in CRC incidence and related mortality. Furthermore, multiple screening strategies and intervals can be compared in real time.

In the present study, we used clinical effectiveness modeling to assess the projected decrease in CRC incidence and related mortality

with mt-sDNA-based CRC screening when used at 1-, 3-, and 5-year screening intervals. We compared the projected decrease in CRC incidence and related mortality to the rates with optical colonoscopy performed every 10 years, the reference method.<sup>9,10</sup> Our findings provide quantitative modeling data to help support the inclusion of mt-sDNA testing in CRC medical policy statements and screening guidelines.

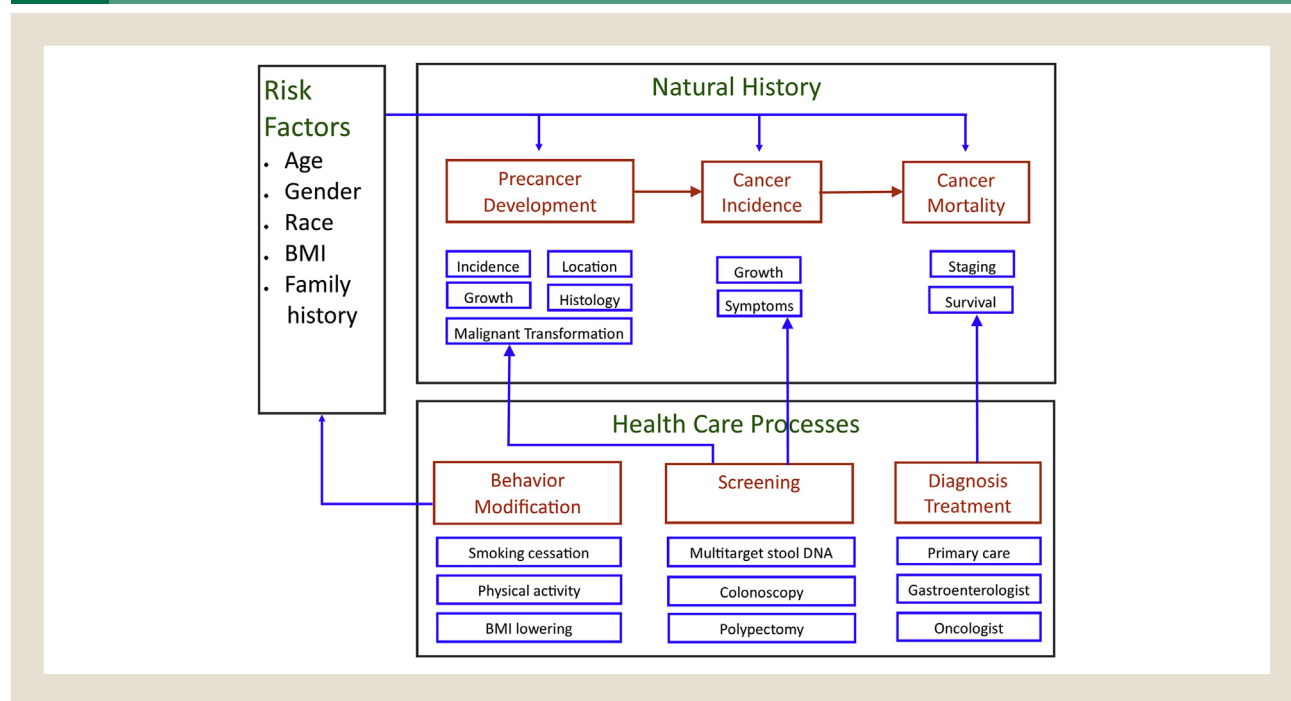
## Materials and Methods

### Model

The Archimedes model (Archimedes Inc., San Francisco, CA) was used to conduct a 5-arm virtual clinical screening study comparing the effect of 4 screening strategies (Cologuard at a 1-, 3-, or 5-year interval or colonoscopy at a 10-year interval) versus “no screening” (Figure 1; see also Supplemental Appendix 1 in the online version).<sup>12</sup> The Archimedes model is a largescale integrated simulation model. Its core is a set of algebraic and differential equations that represent physiology, disease states, and health care processes (systems). The CRC submodel represents those aspects of the anatomy and physiology pertinent to CRC and its complications.

The Archimedes model was built with empirical data derived from systematic published data searches in MEDLINE, Cochrane Database of Systematic Reviews, PubMed, Web of Science, and Google Scholar, supplemented with manual searches. CRC-specific modeling data were derived from clinical trials, retrospective analyses, population surveys, and cancer registries, including colonoscopy data from the Clinical Outcomes Research Initiative database and clinical incidence data from the Surveillance Epidemiology and

**Figure 1** The Archimedes Model. The Model Evaluates Virtual People, Who Can Experience  $\geq 1$  Disease States, Undergo Screening and/or Develop Symptoms, Seek Care, and Receive Diagnosis and Treatment



Abbreviations: BMI = body mass index; FOBT = fecal occult blood test.

End Results program. This model has been validated in a similar manner to other well-published CRC screening models used by the Cancer Intervention and Surveillance Modeling Network consortium, including MISCAN and simCRC (available at <http://cisnet.cancer.gov/profiles/>), using the National Polyp Study, Minnesota FOBT (fecal occult blood test) Screening Trial, Cancer Prevention Study II Nutrition Cohort, Women's Health Study, Women's Health Initiative, UK Flexible Sigmoidoscopy Trial, and Veterans Affairs Cooperative Study Group (see [Supplemental Appendix 1](#) in the online version).

The model creates a population of virtual individuals, each of whom has a simulated physiology, experiences  $\geq 1$  disease states, develops symptoms, seeks care, and is diagnosed and treated. The virtual population is rendered representative of real people because it uses genuine person-specific data from the National Health and Nutrition Examination Survey. This ensures that the distributions and correlations of all important variables are the same in the simulated and actual populations. In our study, a population of 200,000 virtual individuals was assigned to 1 of 5 study arms for a 30-year period. Screening started at age 50 and ended at age 85, with screening benefits accruing until the virtual subject died or 30 years had elapsed from study entry.

The model includes 3 components: (1) a natural history component that tracks adenoma development, growth, and progression to cancer and the development of any signs or symptoms as a function of age, gender, race/ethnicity, obesity, physical activity, and family history; (2) a screening component that allows for the detection and removal of adenomas and the diagnosis of preclinical (asymptomatic) CRC; and (3) a treatment component that predicts survival after the diagnosis of CRC. The model accounts for important risk factors for CRC, including age, gender, race, and body mass index ([Figure 1](#)). Subject adherence was set at 100% for all screening and follow-up tests.

### Subjects and Screening Strategies

**No Screening.** In the control arm, subjects did not receive any screening during the 30-year period ("no screening"). Individuals developing advanced CRC precursor lesions or CRC were removed from the screening pool.

**mt-sDNA Screening.** mt-sDNA screening performance data for Cologuard were taken from a recently completed 10,000-patient, multisite, screening study of average-risk patients.<sup>7</sup> That study had compared Cologuard with fecal immunochemical testing (FIT) using colonoscopy of all subjects as the reference method.<sup>7</sup> Cologuard sensitivity was 92% for CRC (American Joint Committee on Cancer stages I-IV)<sup>7</sup> and 66% for adenomas  $\geq 2$  cm and 42% for adenomas  $\geq 1$  cm; the specificity was 87%.<sup>7</sup> For the calculation of specificity, true-positive cases included only subjects with CRC or adenomas or sessile serrated polyps of  $\geq 1$  cm and those with adenomas of any size with high-grade dysplasia or a villous component of  $\geq 25\%$ .

In the model, subjects with "negative" Cologuard results were screened again at 1-, 3-, or 5-year intervals until the end of the study or until their test results turned "positive." The subjects with "positive" results were referred for diagnostic colonoscopy. The subjects with positive (abnormal) findings on diagnostic

colonoscopy were treated or underwent colonoscopic surveillance according to the current guidelines.<sup>10</sup> Subjects with "negative" findings on diagnostic colonoscopy were returned to the screening pool after 10 years and continued with colonoscopy screening.<sup>7</sup> A Cologuard test cost of \$600 was used in the model.

**Colonoscopy.** The colonoscopy performance characteristics were derived from a review of the published data (see [Supplemental Appendix 2](#) in the online version) and included a sensitivity of 95% for CRC and 90% for adenomas  $\geq 1$  cm and a specificity of 90%.<sup>13</sup> Subjects with abnormal findings on the screening colonoscopy were treated or underwent colonoscopic surveillance according to the current guidelines. Subjects with "negative" findings were returned to the screening pool after 10 years and continued with colonoscopy screening. A colonoscopy cost of \$1500 was used in the model (see [Supplemental Appendix 2](#) in the online version).

**Endpoints.** We used a decrease in CRC incidence and related mortality as the clinical effectiveness endpoints for the modeled strategies. In addition, cost-effectiveness ratios (CERs) in US dollars per quality-adjusted life year (\$/QALY) were calculated for each modeled interval compared with no screening. The CERs were calculated from a societal perspective using published data sources for quality adjustments and cost (see [Supplemental Appendix 2](#) in the online version).

## Results

The theoretical anticipated decrease in CRC incidence and mortality resulting from each of the 4 different screening strategies compared with the no screening control arm is listed in [Table 1](#). Compared with no screening, colonoscopy every 10 years was associated with a 65% decrease in CRC incidence and a 73% decrease in CRC-related mortality, with a gain of 0.1330 QALY. Annual mt-sDNA testing with Cologuard was associated with a 63% decrease in CRC incidence and a 72% decrease in CRC-related mortality, with a gain of 0.1290 QALY. Screening every 3 years with mt-sDNA testing was associated with a 57% decrease in CRC incidence and a 67% decrease in CRC-related mortality, with a gain of 0.1160 QALY. Finally, screening every 5 years with

**Table 1** Effect of Screening Strategies on CRC Incidence and Related Mortality Compared With No Screening

CRC Screening Strategy	Screening Age 50-85 Years		
	Decrease in CRC Incidence (%)	Decrease in CRC Mortality (%)	QALY Gained Relative to No Screening
No screening	0	0	0
Colonoscopy every 10 years	65	73	0.1330
mt-sDNA annually	63	72	0.1290
mt-sDNA every 3 years	57	67	0.1160
mt-sDNA every 5 years	52	62	0.1050

Abbreviations: CRC = colorectal cancer; QALY = quality-adjusted life year; mt-sDNA = multitarget stool DNA (test).

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mt-sDNA testing was associated with a 52% decrease in CRC incidence and a 62% decrease in CRC-related mortality, with a gain of 0.1050 QALY.

Compared with no screening, screening every 1, 3, and 5 years with Cologuard resulted in a CER of \$20,178/QALY, \$11,313/QALY, and \$7388/QALY, respectively (Table 2).

## Discussion

We used the Archimedes CRC model to perform a virtual clinical study to examine the theoretical clinical effectiveness of a new mt-sDNA CRC screening test on reducing CRC incidence and related mortality. We compared the differential clinical effectiveness of Cologuard when used at 1-, 3-, and 5-year intervals with no screening and with colonoscopy every 10 years and calculated the cost-effectiveness of each interval and colonoscopy every 10 years compared with no screening.

Setting an effective and achievable test interval depends on both the performance of the screening test and the ability of patients, clinicians, and administrative infrastructures to maintain the recommended schedule. Our modeling results suggest that annual Cologuard testing would provide a reduction in CRC incidence and mortality similar to that of colonoscopy every 10 years. However, clinical experience has indicated that adherence to annual CRC screening (with fecal occult blood testing or FIT) is low in both clinical practice<sup>14-19</sup> and clinical trial settings.<sup>20</sup> Gellad et al<sup>14</sup> reported only 13% to 14% adherence to consecutive annual fecal occult blood testing during a 4- to 5-year period in an integrated Veterans Affairs health system supported by an electronic medical record. Improvement in adherence rates is possible with aggressive clinical and administrative management. For example, a highly integrated private health care delivery system supported by a central

electronic medical record achieved 50% to 60% adherence with annual, single-sample FIT testing with a 5-year follow-up period.<sup>21</sup> However, this system requires significant resources. In primary care environments that lack direct patient call centers, electronic medical record–based reminders, and tracking systems and have limited office staff, annual screening might not be achievable. Furthermore, few patients prefer annual testing.<sup>22</sup>

The greater point sensitivity of Cologuard relative to FIT for the detection of CRC (92.3% vs. 72.7%) and advanced precancerous lesions (42.4% vs. 23.8%) supports a less-frequent screening interval for Cologuard than for FIT.<sup>7</sup> Screening at a less-frequent interval also has the potential to increase adherence, which could also serve to decrease the burden on both patients and physician practices. Our modeling results showed that testing every 3 years with Cologuard provided sufficient clinical effectiveness for the detection of CRC, decreasing the CRC incidence by 57% and reducing CRC-related mortality by 67%. Although a 5-year Cologuard test interval could further lower the clinical and administrative burden of testing, the clinical effectiveness was substantially lower than that of colonoscopy every 10 years.

Screening study data<sup>7</sup> have similarly supported a Cologuard multiyear interval with a negative predictive value of a single test event of 99.94% for CRC and 95% for advanced adenoma. These data suggest that the presence of missed significant lesions before the next scheduled screening event would be rare.

We also assessed the cost-effectiveness of Cologuard at various intervals relative to no screening to examine the economic acceptability of each screening interval. The CERs of mt-sDNA screening performed every 1, 3, or 5 years compared with no screening were all cost-effective relative to a conservative willingness-to-pay threshold of \$25,000/QALY.<sup>23</sup> All modeled Cologuard and colonoscopy screening CERs compared favorably with those of other common cancer screening tests that have been compared with a no screening strategy, including annual or triennial Papanicolaou smears<sup>24</sup> (\$23,900/QALY and \$15,500/QALY, respectively) and mammography (\$30,000/QALY biennial for women aged 50-75 years, \$32,307/QALY biennial for women aged 40-80 years, and \$39,210/QALY annual for women aged 40-80 years; Table 2).<sup>25</sup> The use of CERs compared with no intervention allows for comparisons of a broad range of medical interventions deemed of societal benefit. Modeling studies using empirical data to explore the effect of differential adherence of CRC screening strategies will be important in examining incremental cost-effectiveness ratios (ICERs) in CRC screening.

The primary focus of the present analysis was to evaluate the intertest interval for mt-sDNA testing as a screening option for CRC. Colonoscopy remains the reference standard for CRC screening. We did not consider ICER modeling across a broad range of CRC screening tests, because the utility of the ICER is limited by the assumption that all tests will be equally acceptable to patients. This mt-sDNA test was developed precisely because colonoscopy is unacceptable to a subset of patients. Patient preference plays a strong role in CRC screening uptake and adherence and thus on the achievable performance of the screening program. Patient preference can be driven by various factors, including test accuracy, test frequency, and the invasiveness of the test. Some patients prefer the most accurate test, but others will prefer the least invasive and others the least

**Table 2** CERs of mt-sDNA Screening at Intervals of 1, 3, and 5 Years Compared With No Screening and in Relation to Other Cancer Screening Tests With No Screening Comparators

Variable	CER (\$/QALY)
CRC screening strategy	
No screening	\$0
mt-sDNA annually	\$20,178
mt-sDNA every 3 years	\$11,313
mt-sDNA every 5 years	\$7388
Cervical (Papanicolaou smear) and breast cancer (mammography) screening strategy	
Pap smear, annual <sup>24</sup>	\$23,900
Pap smear, triennial <sup>24</sup>	\$15,500
Mammography, biennial, aged 50-75 years <sup>25</sup>	\$30,000
Mammography, biennial, age 40-80 years <sup>25</sup>	\$32,307
Mammography, annual, age 40-80 years <sup>25</sup>	\$39,210

Abbreviations: CERs = cost-effectiveness ratios; CRC = colorectal cancer; QALY = quality-adjusted life-year; mt-sDNA = multitarget stool DNA (test).

<sup>a</sup>CER expressed as US dollars/QALY.



frequent.<sup>19,22</sup> Although colonoscopy is the most accurate and least frequent CRC screening method, it is also the most invasive, necessitates a time commitment from patients (including the potential for missed work), and requires preprocedure bowel preparation, sedation during the procedure, and a chaperone for transport after the procedure.<sup>10</sup> Colonoscopy can also be associated with complications such as perforation and postpolypectomy bleeding.<sup>10</sup> In contrast, mt-sDNA testing is less invasive but is also less sensitive than colonoscopy and requires patient cooperation for home sample collection. Thus, we did not view mt-sDNA and colonoscopy as having equal acceptability for patients undergoing CRC screening but rather as compatible screening options for different patient archetypes.

Approximately 35% of the population aged 50 to 75 years who are eligible for CRC screening remain unscreened,<sup>2</sup> despite the availability of multiple CRC screening tests and physician recommendations for screening. In particular, the compliance rates with colonoscopy have remained low.<sup>2,3</sup> Inadomi et al<sup>15</sup> found that only 38% of subjects recommended for colonoscopy actually completed the screening within 12 months. However, a subset of patients might be willing to be screened using other, less-invasive tests (eg, mt-sDNA testing) who otherwise might not be willing to undergo screening. This was suggested by the results from Berger et al,<sup>26</sup> who reported that 52% of subjects who used an earlier, less-sensitive mt-sDNA test had never previously undergone screening. A sensitive test that is noninvasive and has an acceptable CER compared with no screening could provide an important alternative for patients who have refused other CRC screening modalities such as colonoscopy.

The present study was limited by several factors. First, the model assumed 100% adherence for all screening strategies during a 30-year period aged 50 to 85 years. Clinical experience suggests that patient acceptance of, and adherence to, different screening strategies will be dependent on many factors and variables. The model output, therefore, might have overestimated the actual clinical benefit of CRC screening strategies with respect to CRC incidence and mortality reduction. Second, recent observations and insights into the biology of colorectal carcinogenesis<sup>27</sup> and the performance of colonoscopy, in general,<sup>4,5,27</sup> and on proximal versus distal advanced colorectal neoplasia, in particular,<sup>28-31</sup> have not yet been incorporated into currently published CRC disease state models, which could affect the model outcomes. Third, with respect to cost-effectiveness, the cost of colonoscopy varies significantly across providers and payors, and the cost used in our model might not reflect the cost for a specific payor. Similarly, the cost of therapy will continue to increase over time with the increased use of biologic agents and the migration of postoperative chemotherapy to lower stage disease. The cost used in our model might have underestimated the cost of treatment and therefore underestimated the screening cost-effectiveness.

## Conclusion

The present modeling study assessed the effect of the screening interval for mt-sDNA testing with Cologuard on CRC incidence and related mortality. The modeled results showed that a 3-year mt-sDNA test interval provides a decrease in CRC incidence and mortality that is lower than that of colonoscopy every 10 years during a 30-year screening period but still clinically acceptable and cost-effective at a \$25,000/QALY willingness-to-pay

threshold. Although the screening performance of a 3-year interval was less effective than an annual interval, it is likely to be more achievable because of clinical practice and patient preference factors and the greater cost-effectiveness. A 5-year interval was more cost-effective than the 3-year interval but sacrificed additional performance. A 3-year Cologuard test interval seems to provide reasonable performance at acceptable costs with a lower patient, clinician, and administrative burden than annual screening and with improved clinical performance compared with 5-year screening. These results support the current expert opinion-based recommendation of a 3-year screening interval for sDNA according to the American College of Gastroenterology<sup>9</sup> and the Centers for Medicare and Medicaid as per the American Cancer Society<sup>32</sup> guidelines and the Centers for Medicare and Medicaid Services coverage policy.<sup>33</sup>

## Clinical Practice Points

- The Food and Drug Administration recently approved mt-sDNA testing for CRC screening.
- The current guidelines recommend a 3-year interval for mt-sDNA screening but without empirical data available.
- A virtual clinical study using modeling examined the clinical effect of 1-, 3-, and 5-year intervals.
- A 3-year interval appeared to be clinically effective at reasonable cost.

## Acknowledgments

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## Disclosure

Dr. Barry M. Berger is an employee of Exact Sciences Corporation, Dr. Tuan Dinh is an employee of Archimedes, Dr. Paul Schroy declares that he has no competing interests.

## Supplemental Data

The supplemental data accompanying this article can be found in the online version at <http://dx.doi.org.10.1016/j.clcc.2015.12.003>.

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## Appendix 1: The Archimedes Model

The Archimedes model is a largescale, integrated simulation model of human physiology, diseases, and health care delivery processes that includes a colorectal cancer (CRC) submodel.<sup>1,2</sup> The model core is a set of algebraic and differential equations that represent physiology, disease states, and health care processes (systems). The CRC submodel represents those aspects of the anatomy and physiology pertinent to CRC and its complications. The Archimedes model creates virtual people, each of whom has a simulated physiology and can experience  $\geq 1$  disease states, develop symptoms, seek care, and receive diagnosis and treatment. Virtual people are rendered representative of real people with actual person-specific data from the National Health and Nutrition Examination Survey. The methods for creating copies ensure that the distributions and correlations of all important variables in the simulated population are the same as those in the real population.

The CRC submodel, developed in collaboration with the American Cancer Society and an expert panel, was built with empiric data derived from systematic published data searches in MEDLINE, Cochrane Database of Systematic Reviews, PubMed, Web of Science, and Google Scholar, supplemented with manual reference searches. CRC-specific modeling data were derived from clinical trials, retrospective analyses, population surveys, and cancer registries. The model also includes individual-level colonoscopy data from the Clinical Outcomes Research Initiative database<sup>3</sup> and clinical incidence data from the Surveillance Epidemiology and End Results program.<sup>4</sup>

The model includes (1) a natural history component that tracks adenoma development, growth and progression to cancer, and the development of any signs or symptoms as a function of age, gender, race/ethnicity, obesity, physical activity, and family history; (2) a screening component that allows for the detection and removal of adenomas and the diagnosis of preclinical (asymptomatic) CRC; and (3) a treatment component that predicts survival after the diagnosis of CRC. The model accounts for important risk factors of CRC, including age, gender, race, and body mass index.

Both non-neoplastic polyps (hyperplastic polyps) and neoplastic polyps (conventional adenomas and sessile serrated adenomas [SSAs]) with the potential to progress to CRC are modeled. By modeling both types, the precision of the model can be compared with empirical data sources for validation.

In the model, polyps arise in the colon and the rectum stochastically through a nonhomogenous Poisson process.<sup>5</sup> The incidence of polyps increases with age and is a function of the aforementioned risk factors. Polyps can occur at 8 different anatomic sites: cecum, ascending colon, hepatic flexure, transverse colon, splenic flexure (collectively, the “right” or proximal colon), descending colon, sigmoid colon, and rectum (collectively the “left” or distal colon). The growth of hyperplastic polyps and adenomas is modeled using a log-linear equation. As an adenoma grows, its histologic features and grade will worsen. On average, conventional adenomas and SSAs are larger than hyperplastic polyps. The propensity of an adenoma to become cancerous is assumed to be a function of age and adenoma type, size, and location. Once an adenoma becomes cancerous, it will grow exponentially, with a doubling time derived from a meta-analysis of the published data.<sup>6-9</sup>

When it reaches a certain size, the patient will begin to experience CRC signs or symptoms and, after a delay period, will be diagnosed by the health care system with symptomatic CRC. The distribution of CRC size at diagnosis of symptomatic CRC has been derived from early Surveillance Epidemiology and End Results (SEER) data<sup>4</sup> to minimize the effects of screening. If the patient undergoes screening, the CRC will be detectable earlier, before symptoms develop. The performance of a test (ie, FIT, stool DNA [sDNA], or colonoscopy) depends on the size, type, and location of polyps.

The CRC outcomes predicted by the Archimedes model have been validated against several studies, including the National Polyp Study,<sup>10</sup> Minnesota FOBT (fecal occult blood test) Screening Trial,<sup>11</sup> Cancer Prevention Study II Nutrition Cohort,<sup>12</sup> Women’s Health Study,<sup>13</sup> Women’s Health Initiative,<sup>14</sup> UK Flexible Sigmoidoscopy Trial,<sup>15</sup> and Veterans Affairs Cooperative Study Group.<sup>16</sup>

### Screening Simulation Setup

The effectiveness of CRC screening by multitarget sDNA test (3 intervals) and colonoscopy every 10 years was compared by conducting a virtual trial, which subjected a population of virtual individuals to different trial arms (screening strategies). For each strategy, screening started at age 50 years, ended at 85 years, and had the compliance set at 100% (ie, 100% rate of adoption) for all arms, except for the control arm (no screening). Patients with positive (abnormal) results by multitarget sDNA testing underwent diagnostic colonoscopy at 100% compliance. Those found to have developed precursor lesions, advanced adenomas (adenomas  $\geq 1$  cm or with high-grade dysplasia or  $\geq 25\%$  villous component of any size), or CRC were removed from the screening pool. For this exercise, those patients with small, nonadvanced adenomas ( $< 1$  cm) were treated similarly to the treatment of patients with negative (normal) findings, remained in the screening pool and were screened thereafter using colonoscopy after the 10-year colonoscopy intertest interval had elapsed.

An estimate of cost-effectiveness was also undertaken to provide economic context. The cost-effectiveness ratio (CER) of CRC screening with multitarget sDNA strategies (\$600/test) compared with no screening was determined. A low willingness-to-pay threshold of \$25,000 was considered cost-effective.

### Cost of CRC Treatment

The CRC treatment costs were adapted from estimates based on data from the SEER and published sources.<sup>17</sup> Cancer treatment costs are divided into 3 phases: initial, continuing, and final phases. The initial phase of care is defined as the first 12 months after the diagnosis, the last-year-of-life phase is the final 12 months of life, and the continuing phase is all the months between the initial and last-year-of-life phases. For patients who survive  $< 24$  months after diagnosis, the final 12 months of observation and costs of care were allocated first to the last-year-of-life phase, because the content of care for patients with short survival will more similar to the last-year-of-life phase than to the initial phase. The remaining months of observation and costs were allocated to the initial phase, with no contribution to the continuing phase. The cancer-related costs in the continuing phase were an annual estimate.

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All costs were adjusted to 2010 values using the medical care component of the Bureau of Labor Statistics Consumer Price Index.<sup>18</sup> The health utility scores for different the CRC outcomes were derived from Ness et al.<sup>19</sup> For each sDNA strategy, the CER was calculated compared with no screening.

## Quality-of-life Adjustments for CRC Diagnosis

The quality-of-life parameters for the calculation of quality-adjusted life years were derived from the published data<sup>19</sup> and are reported in Table 1.

## Perspective

A societal perspective was used, with costs, benefits, and life years discounted 3% and with adherence to other recommendations of the Panel on Cost-Effectiveness in Health and Medicine.<sup>20</sup> The effects of discount rate, patient adherence, and cost of colonoscopy on the cost-effectiveness of the CRC screening strategies through sensitivity analysis were explored.

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## Appendix 2 Archimedes Model Assumptions

Parameter	Assumptions and Approaches		
Natural history of CRC			
Polyp type	Three major types of polyps were modeled: HPs, conventional adenomas, and SSAs		
Adenoma incidence	Adenoma incidence was assumed to follow a nonhomogenous Poisson distribution <sup>1</sup>		
	Effects of gender, family history, BMI, aspirin, hormonal replacement therapy, and diabetes on incidence of HPs, conventional adenomas, and SSAs represented by HRs derived from author-conducted meta-analyses <sup>2-30</sup>		
Adenoma growth	Growth of adenomas described with a Gompertzian growth equation; at initiation, adenoma size was assumed to be 1 mm		
	Adenoma growth rate was modeled as a function of age, gender, and race and calibrated to CORI data and other published colonoscopy screening studies <sup>31-41</sup>		
	Size distribution of HPs, conventional adenomas, and SSAs at colonoscopy was matched to the CORI database and meta-analysis of published studies <sup>40,42-46</sup>		
Adenoma location	Adenomas can occur at 8 different anatomic sites along the colon and rectum (ie, cecum, ascending colon, hepatic flexure, transverse colon, splenic flexure, descending colon, sigmoid colon, and rectum)		
	Distribution of anatomic sites of conventional adenomas and HPs as a function of age and gender were extracted from the CORI database and were consistent with the published data <sup>47,48</sup> ; distribution of SSAs was based on a meta-analysis <sup>4,30,42,49</sup>		
Adenoma histologic features and dysplasia grade	Histologic features and grade of dysplasia are functions of adenoma size and were determined from an author-conducted meta-analysis <sup>3,50-53</sup>		
Cancer risk and malignant transformation	Hazard rate of an adenoma becoming malignant is a function of age, gender, and adenoma location		
	The form of the hazard rate was derived from an author-conducted meta-analysis <sup>41,54-57</sup> ; the parameters were obtained by fitting the hazard rate to the CORI and SEER databases		
Cancer progression	Progression of tumors from stage 0 to IV was calibrated to SEER data and stage distribution data obtained from screening studies <sup>58-62</sup>		
Cancer diagnosis and survival	Patient survival is a function of age and tumor characteristics at diagnosis and was derived from the SEER database		
	Effect of diabetes on CRC-specific survival was modeled using data from a meta-analysis		
Test characteristics			
Colonoscopy	CRC 95% sensitivity (range, 90%-99%)		
	Adenoma by size		
	0-5 mm: 70% sensitivity (range, 65%-75%)		
	5-10 mm: 80% sensitivity (range, 75%-85%)		
	≥ 10 mm: 90% sensitivity (range, 85%-95%)		
	CRC and advanced adenoma: 95% specificity		
	Completion rate: 97%		
	Proximal lesions: 75% <sup>63</sup>		
	Miss rate for SSAs: 50% (indirect evidence of SSA prevalence and detection rates in colonoscopy screening studies)		
Adverse events associated with colonoscopy	Perforation and surgical mortality are a function of age and comorbidities and were derived from author-conducted meta-analysis		
Costs			
Colonoscopy without polypectomy	\$1500 <sup>64</sup>		
Colonoscopy with polypectomy or biopsy	\$1700 <sup>64</sup>		
CRC treatment	CRC treatment costs were estimated for initial, maintenance, and terminal phases, including costs of targeted therapies		
Disease stage	Initial	Maintenance	Terminal
I	\$34,963	\$2921	\$136,514
II	\$48,417	\$2728	\$136,242
III	\$97,324	\$3962	\$139,979
IV	\$97,324	\$12,707	\$162,877
Treatment and prevention of other diseases, including DM complications and CVDs	Medication costs were obtained from <a href="http://drugstore.com">drugstore.com</a> as of April 2009		
	All other costs (eg, emergency visits, office visits and admissions, and procedures) were based on 2007 Medicare reimbursement rates		
Health utility			
CRC stage <sup>65</sup>	Health disutility for colorectal cancer		
I	0.74		
II	0.67		
III	0.50		
IV	0.25		
Other diseases	Utility scores used: Sullivan and Ghushchyan <sup>29,30</sup>		

Abbreviations: BMI = body mass index; CORI = Clinical Outcomes Research Initiative; CRC = colorectal cancer; CVD = cardiovascular disease; DM = diabetes mellitus; HP = hyperplastic polyp; HR = hazard ratio; SEER = Surveillance Epidemiology and End Results; SSA = sessile serrated adenoma.

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